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The Control of The Inflammatory Response as The Fundament of All Types of Medical Therapies: The Anti-Inflammatory Action of Pineal Gland, Cannabinoid System, Melanocortin System and Ace2-Angiotensin 1-7 Axis.

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Abstract

The immune response is constantly associated with an inflammatory reaction, which, if excessive, may suppress the immune response. The endothelium is directly or indirectly involved in all inflammation-related pathologic processes. Then, the regulation of the biological characteristics of the endothelial cells, including their inflammatory, thrombotic, fibrotic and angiogenic properties, is fundamental to control the clinical evolution of human systemic inflammatory diseases. Most cytokines play inflammatory activities. Therefore, the control of the inflammatory status is mainly exerted by the neuroendocrine system, particularly by the brain cannabinoid-pineal gland axis and by the melanocortin system through the release of alpha-MSH. However, the two systems are characterized by opposite effects on the antitumor immunity, which is stimulated by the pineal-cannabinoid axis and inhibited by the melanocortin system. Moreover, endothelial cells themselves may regulate their biological characteristics through the preferential production of angiotensin II (Ang II) of angiotensin 1-7 (Ang 1-7), due to the enzymatic action of ACE and ACE2, respectively. Ang II and Ang 1-7 are characterized by opposite effects. In fact, Ang II plays hypertensive, inflammatory, pro-tumoral, angiogenic, pro-thrombotic and fibrotic effects, whereas Ang 1-7 has appeared toexert hypotensive, cardioprotective, anti-inflammatory, ani-tumor, anti-angiogenic, anti-thrombotic and anti-fibrotic effects. The main link between cytokine network and the cardiovascular system would be represented by the inflammatory cytokine IL-17, produced by Th17 lymphocytes, which has been proven to promote Ang IIsecretion by stimulating ACE expression, to suppress Ang 1-7 production, and to exert direct toxic vascular effects. The neuroendocrine control of the inflammatory response could constitute a new approach in the therapy of inflammation-related human system diseases.

Key Words: ACE2; angiotensin ii; angiotensin 1-7; cannabinoid system; inflammatory status; melanocortin system; melatonin.

Introduction:

Irrespectively of the type of pathology, all systemic human diseases, including cancer, autoimmunity and metabolic syndrome, and the neurodegenerative diseases, recognize a common mechanism, represented by the inflammatory status. The recent advances in the immunology have shown that the inflammation is essentially induced by the cytokine network through the release of inflammatory cytokines from activated lymphocytes and monocytes, the most important of them consist ofIL-1beta, IL-6, IL-8, IL-17 and TNF-alpha. Then, the inflammatory cytokines determine the inflammatory status by inducing the local production of several mediators of the inflammation, including chemokines, prostaglandins, leukotrienes, and P substance. Therefore, it is possible to regulate the inflammatory response by acting either at central level on cytokine network itself, or at peripheral level through an inhibition of prostaglandin and leukotriene production. Unfortunately, within the group of more than 40 cytokines, most of them are characterized by inflammatory activity, whereas only few cytokines

may play an evident anti-inflammatory action, namely TFG-beta, IL-10, and IL-35 [1]. Therefore, the control of the prevalent inflammatory action of the cytokine network is mainly realized by a neuroendocrine anti-inflammatory functional axis, which is fundamentally constituted of five major systems, represented by cannabinoid system [2], pineal gland [3], melanocortin system (4), heart endocrine activity through the release of the atrial natriuretic peptide (ANP) [5], and ACE2-angiotensin 1-7 (Ang 1-7) axis [6]. Then, each deficiency involving brain cannabinoid system, pineal gland, melanocortin system, heart endocrine function, and ACE2 activity, may predispose to the onset of an enhanced inflammatory status, and the consequent related diseases.

The Anti-Inflammatory Action of The Pineal Gland:

The main function of the pineal gland is the transduction of the universal energetic condition into a modulation of the biological life, including the biological rhythms, the cardiovascular function, and the immune status [3]. The pineal is generally known for the only MLT [7]. In contrast, in addition to the indole MLT, it produces three other indoles in relation to the different phases of the photoperiod, consisting of 5-methoxytryptamine (5-MTT), 5-methoxytryptophol, and 5-mehoxy-indole acetic [8], and more than ten beta-carbolines, generated by an indoleamine in association with an aldehyde, the most known of them is the 6-methoxy-1,2,3,4-tetrahydro-beta-carboline, the so-called pinealine [9]. MLT, 5-MTT and beta-carbolines have appeared to exert an important antitumor and anti-inflammatory activity by regulating the cytokine network. In fact, the pineal gland may be considered the central regulator of the cytokine network, by regulating the immune system in relation to the universal conditions [10]. At present, however, the mechanisms of action have been established for the only MLT, which has been shown to stimulate dendritic cell activation with a following enhanced IL-12 secretion, and Th1 lymphocyte function with a consequent enhanced production of IL-2 [11], and to inhibit IL-17 secretion [12]. The stimulation of IL-2 and IL-12 secretion may explain its anticancer activity, being the two main anticancer cytokines in humans [13,14], while its anti-inflammatory action would mainly depend on the inhibitory action on IL-17 secretion [12], as well as on macrophage-related inflammatory cytokines, including TNF-alpha and IL-6 [11]. Despite its immunostimulatory action, MLT would be also effective in the treatment of autoimmune diseases, since they are mainly due to an enhanced IL-17 production.

The Physiology of Cannabinoid System:

The cannabinoid group is constituted by two classes of molecules, which consist of cannabinoid agonists and inhibitors of fatty acid amide hydrolase (FAAH), the enzyme involved in cannabinoid degradation, with a consequent increase in cannabinoid endogenous content [2]. The main endogenous cannabinoid agonists are represented by arachidonyl-ethanol-amide (AEA) and 2-arachidonyl-glycerol (2-AG), while the main cannabinoid agonist from Cannabis is the tetrahydrocannabinol (THC). The main FAAH inhibitors from human body and Cannabis are represented by palmitoyl-ethanol-amide (PEA) and cannabinol (CBD), respectively. Both cannabinoid agonists and FAAH inhibitors play an anti-inflammatory activity due to an inhibition of IL-17 secretion. They have also appeared to exert an anticancer action, even though through different mechanisms, since cannabinoid agonists may play a direct cytotoxic antiproliferative anticancer action, while FAAH inhibitors mainly act by enhancing the endogenous cannabinoid content. Human systemic diseases could be characterized by an endogenous cannabinoid deficiency [15]. The cannabinoid system has appeared to be connected to the pineal function, by constituting a functional axis involved in the control of cell proliferation and inflammatory status [16]. The neurohypophyseal hormone oxytocin has also been shown to be connected to pineal and cannabinoid system functionless [17]. Then, oxytocin would also contribute to the antitumor and anti-inflammatory action of the pineal and cannabinoid system.

The Anti-Inflammatory Action of The Melanocortin System:

The melanocortin system consists of neurons, mainly located at hypothalamic level, which express the proopiomelanocortin (POMC) [18], the common precursor of several melanocortin-like molecules, including alpha-MSH, ACTH, and beta-endorphin. The molecule most provided by immunomodulating effects would be represented by alpha-MSH, which has appeared to exert an important anti-inflammatory action, mainly due a stimulation of IL-10 secretion. However, because of the immunosuppressive action of IL-10 [1], the anti-inflammatory activity of alpha-MSH may concomitantly induce a suppression of the anticancer immunity. ACTH has also appeared to play a direct anti-inflammatory activity irrespectively of its stimulatory action on cortisol production from the adrenal gland [18].

The Renin-Ace-Ace2 System:

The first step of the system is represented by liver production of angiotensinogen, which is transformed into angiotensin I (Ang I) by the protease renin produced by the renal juxtaglomerular cells. ACE transforms Ang I into angiotensin II (Ang II), which may be furtherly transformed into Ang 1-7 by ACE2. Then, Ang II and Ang 1-7 represents the two major products of ACE and ACE2, respectively [19]. A deficiency of ACE2 allows a diminished endogenous production of Ang 1-7. ACE and ACE2 are widely expressed on cell surface of most tissues, particularly by endothelial cell themselves, by constituting a fundamental regulatory system of the endothelial function, which is involved in all pathologic diseases. ACE and ACE2 are mainly expressed on cell surface, but they may be also detected in the blood circulation [20]. The existence of an ACE-ACE2 system has been also demonstrated at brain level and within the pineal gland [21]. In addition to their actions on the cardiovascular system, Ang II and Ang 1-7 are characterized by opposite biological systemic effects [22]. In fact, Ang II has appeared to induce hypertensive, cardiac hypertrophic, pro-tumoral, pro-angiogenic, pro-inflammatory, pro-thrombotic, and pro-fibrotic effects, whereas Ang 1-7 plays hypotensive, cardioprotective, anti-tumoral, anti-angiogenic, anti-inflammatory, anti-thrombotic, and anti-fibrotic actions. In addition, Ang II has been proven to predispose to the insulin resistance, whereas Ang1-7 may counteract the occurrence of the resistance to insulin [23]. Therefore, the Ang II-to-Ang 1-7 ratio in the blood levels could represent an essential clinical biomarker to establish the inflammatory status of patients.

The Anti-Inflammatory Action of The Heart:

The heart is not only the main organ of life because of its role in determining the possibility of blood circulation, its oxygenation through its connection with the lung, and its purification through its connection with liver and kidney, but also because of its fundamental central regulatory role on the inflammatory status of human body through the release of ANP [5], which in addition to its hypotensive, diuretic and cardioprotective properties, has recently appeared to play also an anti-inflammatory, anti-angiogenic, antitumoral activity [24]. Moreover, ANP would constitute the terminal mediator of the anti-inflammatory neuroendocrine response, since both the pineal hormone MLT [25] and Ang 1-7 [26] have appeared to stimulate ANP secretion, even though they may also exert direct anti-inflammatory effects. The anti-inflammatory and antitumor action of ANP is counteracted by the inflammatory and pro-tumoral activity of endothelin-1 (ET-1) [27], produced by the endocardium and the endothelial cells, which is also involved in the onset of hypertension and cardiac hypertrophy either through direct mechanisms, or promoting the production and activity of Ang II [28].

The Two Biological Pathways of Life and Death in The Human Body:

If we consider the human body in its unity, it appears that there is a molecule provided by opposite effects in relation to each anti-inflammatory molecule. In fact, the anti-inflammatory action of Ang 1-7 is counterbalanced by Ang II, that of oxytocin by vasopressin, that of ANP by ET-1, and that of pineal-cannabinoid axis by the melanocortin system, which plays a similar anti-inflammatory action, but in association with a pro-tumoral activity, whereas the pineal-cannabinoid axis inhibits cancer growth. Moreover, either pineal-cannabinoid-oxytocin-ANP-Ang 1-7 functional axis, or melanocortin-vasopressin-ET-1-Ang II are connected by reciprocal stimulatory interactions, by constituting two biological pathways provided by opposite effects, respectively consisting of a regeneration or a degeneration of the biological functions. Then, they may represent the pathways of the life and death. From this point of view, human systemic diseases may be reinterpreted as the consequence of a prevalence of the way of death on the way of life, as shown by the evidence of a diminished production of MLT, cannabinoids, oxytocin, and Ang1-7 in most systemic diseases and in association with a concomitant increased secretion of vasopressin, Ang II and ET-1.

The Role of Il-17 In the Connection Between Cytokine Network and Cardiovascular System:

IL-17, namely its IL-17A isoform, would represent the main inflammatory cytokine, because of its direct inflammatory effects and its stimulation of macrophage-related cytokines [29]. IL-17 would also constitute the main link between cardiovascular system and cytokine network, since it has appeared to induce vascular damage and cardiotoxicity either directly [30] or by stimulating ACE expression and inhibiting that of ACE2 [31], with a consequent enhanced production of Ang II and diminished secretion of Ang 1-7. Ang II, ET-1, and IL-17 would be connected by reciprocal stimulatory effects [32]. Then, each of them would enhance the cardiovascular toxicity of the other agents. In addition to its inflammatory action, IL-17 has also appeared to exert a pro-tumoral role, due to a direct stimulation of cancer cell proliferation and angiogenesis [33]. Finally, the first immune event responsible for the development of autoimmune diseases is constituted by an enhanced production of IL-17 [34], because of its inhibitory effect on the regulatory T cells, with a consequent diminished inhibitory control of possible autoreactive lymphocytes.

Inflammation and Human Diseases:

All systemic inflammatory diseases, including cancer and autoimmunity, and metabolic syndrome itself have appeared to be characterized by a diminished pineal function in association with a reduced endogenous production of Ang 1-7 and an enhanced endogenous production of Ang II [6,22]. Age-related increased inflammatory status has also been proven to be associated with a progressive increased endogenous production of IL-17 [35], which would be the consequence of the progressive age-related decline in the pineal function [36], then in the MLT production, and in ACE2 expression [37], then in the endogenous production of Ang 1-7. Finally, neurodegenerative diseases would also be the consequence not only of a neuroinflammatory process, but also of a more generalized systemic inflammatory status [38]. Neuroinflammation itself would mainly be due to an unbalance between ACE and ACE2 expression at brain level [39]. The enhanced production of Ang II at brain level would simulate the glial cells to release inflammatory cytokines, including IL-6 and TNF-alpha. Covid-19 disease would be also due to an acute and severe deficiency of Ang 1-7 following the downregulation of ACE2 expression induced by the link of viral spike protein to ACE2 receptor on cell surface [40]. In fact, all patients, who more frequently may develop severe complications under Covid-19 infection, including hypertensive, diabetic, and obese patients, are characterized by a previous endogenous deficiency in Ang 1-7 production [41].

Conclusions:

The human systemic diseases have appeared to be characterized by a multiple deficiency involving the neuroendocrine anti-inflammatory system, with a diminished production of the pineal hormone MLT, and Ang 1-7 in association with an endocannabinoid deficiency. Therefore, the endogenous administration of MLT, cannabinoids and Ang 1-7 could represent a new neuroimmune approach to control the exaggerated systemic disease-related inflammatory response. An increased endogenous production of Ang 1-7 may be also obtained by the administration of ACE inhibitors and Ang II receptor blockers [42], whose clinical use in the treatment of hypertension has appeared to prevent cancer development [43,44]. Finally, a neuroendocrine control of the inflammatory response may be also achieved by the administration of TGF-beta, IL-10 and alpha-MSH [1,4], but unfortunately, they are all characterized by a concomitant immunosuppressive action on the anticancer immunity.

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